REMARKS

Claims 1, 21, 36, 58, 78, 86, 93, 95, 118, 119, 134, 137, 142, 145, 146, 148-153 and 155-164 were pending of which claims 21, 36, 58, 78, 86, 93, 95, 118, 119, 134, 137, 142 and 145 were withdrawn. In an Office Action dated May 11, 2010, claims 1 and 146, 148-153 and 155-164 were rejected. The Applicants are amending claims 1, 146, 156 and 159, cancelling claims 21, 36, 58, 78, 86, 93, 95, 118, 119, 134, 137, 142, 145, and adding claims 165 and 166. Applicants thank the Examiner for examination of the claims pending in this application and address the Examiner's comments below.

Support for Amendments to the Claims

Claim 1 has been amended to recite, "wherein the therapeutically effective amount of the adenosine receptor antagonist is lower than the therapeutically effective amount of an adenosine receptor antagonist administered without said dopamine receptor antagonist." Support for this amendment is found throughout the application as filed and specifically at claim 1 as originally filed. Claim 146 has been amended to recite, "wherein the therapeutically effective amount of the dopamine receptor antagonist is lower than the therapeutically effective amount of a dopamine receptor antagonist administered without said adenosine receptor antagonist." Support for this amendment is found throughout the application as filed and specifically at claim 146 as originally filed.

Claims 156 and 159 have been amended to clarify antecedent basis issues.

Support for new claim 165 can be found throughout the application as filed and specifically at Figures 22A-22G and 25 and paragraphs [0064] and [0067]. Support for new

claim 166 can be found throughout the application as filed and specifically at Figures 19A-19E and 25 and paragraphs [0061] and [0067].

Response to Rejection Under 35 USC § 112, second paragraph

The Examiner rejected claims 1 and 14 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants consider their invention. The Applicants assume the Examiner meant claim 146 and not claim 14 and are treating the rejection as a rejection of claims 1 and 146. Claims 1 and 146 have been amended. Thus the Applicants submit the claims have been clarified and thus the rejection is now moot.

Response to Rejection Under 35 USC § 103(a)

The Examiner rejected claims 1, 146, 148-153 and 155-164 under 35 USC §103(a) as allegedly being unpatentable over Diamond *et al.* (U.S. Patent No. 5,069,895) ("Diamond") in view of Koch *et al.* (*Behavioural Pharmacology*. 9(1):23-29 (1998)) ("Koch"), Fink *et al.* (Abstract only, *Molecular Brain Research*, 14(3):186-195 (1992)) ("Fink"), Dar (*Brain Research Bulletin*, 55(4):513-520 (2001)) and Beasley et al. (U.S. Patent No. 6,159,963) ("Beasley"). This rejection is now overcome.

A proper rejection under 35 U.S.C. § 103 requires, *inter alia*:

1. a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;

2. a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately;

3. a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and

4. whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

72 Fed. Reg. 57,529 (Oct. 10, 2007)

Claim 1, as amended, recites:

> A method of mitigating one or more symptoms associated with chronic consumption of a substance of abuse by a mammal, wherein said substance of abuse is alcohol, said method comprising:
>
> administering to said mammal a therapeutically effective amount of an adenosine receptor antagonist and a therapeutically effective amount of a dopamine receptor antagonist;
>
> **wherein said therapeutically effective amount of the adenosine receptor antagonist is lower than said therapeutically effective amount of an adenosine receptor antagonist administered without said dopamine receptor antagonist**.

The Applicants have made the surprising discovery that there is a synergy between the dopamine D2 and adenosine A2 receptor-stimulated PKA signaling and thus the claimed invention recites administering to said mammal a therapeutically effective amount of an adenosine receptor antagonist and a therapeutically effective amount of a dopamine receptor antagonist wherein the therapeutically effective amount of the adenosine receptor antagonist

is lower than the therapeutically effective amount of an adenosine receptor antagonist administered without said dopamine receptor antagonist.

The cited references alone or in combination do not disclose all of the limitations of claim 1 because there is no disclosure of administering a therapeutically effective amount of an adenosine receptor antagonist and a therapeutically effective amount of a dopamine receptor antagonist wherein the therapeutically effective amount of adenosine receptor antagonist is lower than the therapeutically effective amount of an adenosine receptor antagonist administered without the dopamine receptor antagonist. Since none of the references disclose administering both an adenosine receptor antagonist and a dopamine receptor antagonist, it is impossible for the references to teach that the therapeutically effective amount of the adenosine receptor antagonist is lower than the therapeutically effective amount of an adenosine receptor antagonist administered without said dopamine receptor antagonist. For this reason alone, the claimed method is patentably distinguishable over the references.

Additionally, the Examiner has not shown that one of ordinary skill in the art would have recognized that the results of the combination of treating with an adenosine receptor antagonist and a dopamine receptor antagonist, that result being that an effective amount of an adenosine receptor antagonist is lower when administered with a dopamine receptor antagonist, were predictable. The Examiner cites the teachings of Koch and Fink as providing motivation for one of ordinary skill in the art to treat mitigating one or more symptoms associated with chronic consumption of a substance of abuse with both an adenosine receptor antagonist and a dopamine receptor antagonist because, according to the Examiner, Koch and Fink disclose a beneficial synergistic effect of adenosine A2 and

dopamine D2 receptors. Office Action at 6. To the contrary, Koch and Fink teach away from this combination.

As recited by the Examiner, the bottom of the second column of page 23 of Koch states, "In functional terms, the interactions between DA D_2 and adenosine A_{2A}, as well as between DA D_1 and adenosine A_1 receptors, seems to be antagonistic which means that the stimulation of adenosine A_1 or A_{2A} receptors inhibits D_1- or D_2-receptor mediated effects." Koch would thus suggest that if one were to treat with an adenosine agonist and a dopamine receptor antagonist, the effective dose of either might be less than if only one is used. Logically, one would not assume that the same would be true of treating with an adenosine receptor antagonist instead of an adenosine receptor agonist. Thus, Koch not only does not suggest the claimed invention, it teaches away from the claimed invention.

Fink does not remedy the deficiency of Koch. Fink merely discloses that D_2 dopamine receptors and A_2 adenosine receptors are co-expressed in a subset of striatal cells. Fink, like Koch, also discloses that the relationship between adenosine receptors and dopamine receptors is antagonistic. The first paragraph of the introduction of Fink (attached as Exhibit A as the Examiner had previously only cited the Abstract of Fink) states that adenosinergic antagonists enhance dopamine-induced hypermotility and that adenosinergic agonists inhibit dopamine-induced hypermotility. So with respect to dopamine-induced hypermotility, the combination of a dopamine receptor agonist and an adenosine receptor antagonist is at least additive. One of ordinary skill in the art would thus not predict that there would be a synergy when administering an adenosine receptor antagonist and a dopamine receptor antagonist. Thus Fink also teaches away from the claimed invention.

In summary, the Examiner has failed to point out any prior art teaching which anticipates or renders obvious the explicit recitation in the language of claim 1, "wherein the effective amount of the adenosine receptor antagonist is lower than the effective amount of an adenosine receptor antagonist administered without said dopamine receptor antagonist." Thus the claims are distinguished over the cited references, either individually or in combination.

Conclusion

Reconsideration of the claims is respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicant's representative at (415) 875-2406.

Respectfully Submitted,

Dated: 10 November 2010 By: /Pauline Farmer-Koppenol/

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